

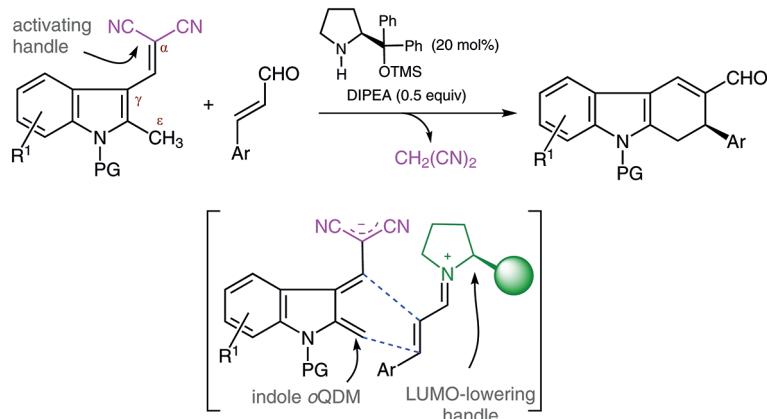
Synform

People, Trends and Views in Chemical Synthesis

2016/12

Exploiting the Distal Reactivity of Indolyl-methylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

Highlighted article by G. Rassu, C. Curti, V. Zambrano, L. Pinna, N. Brindani, G. Pelosi, F. Zanardi



Contact

Your opinion about Synform is welcome,
please correspond if you like:
marketing@thieme-chemistry.com



Dear Readers,

The younger readers will not remember the pioneering era of publishing when authors used to submit their typewritten manuscripts – with hand-made schemes and figures – by surface mail and then feverishly wait for the reply from the editor with the outcome of the evaluation, which sometimes took several months to arrive because everything was done by surface mail, including the correspondence with the reviewers. Those were early days of my academic career, in the 90s, but I still remember those days very well, with mixed sensations and a bit of nostalgia. Now everything is done through the web and by e-mail, so what used to take several weeks can now be done in a few minutes; therefore, one might think that the publishing process has become better and more efficient by a million miles. But has it? Well, I am not so sure... First hurdle of the web submission process are the Guidelines. Yes the Guidelines, often so complex – ten or twenty pages long – that their interpretation has almost become an independent branch of science: Guidelines-ology. Often people get so bored that they decide to take the risk and submit after reading 20% or less of the daunting instructions for authors. Big Mistake! Which comes back to haunt you after just one or two days when you get an e-mail from the journal saying that your paper has been “unsubmitted”. Yes, unsubmitted, because you did not read the Guidelines where – on page 13 and 17 – it is clearly explained that a normal and sensible accompanying letter has been replaced by a 4-pages long preformatted document, that requires hours to be filled, and that a new digitalization system requires the authors to generate grids of obscure strings for each compound described in the manuscript. What??? At that point I normally start swearing and seriously considering a job in administration. And what about the authors list? Each author has to be added individually, with e-mail, address, shoe number and culinary tastes. Normally it takes one hour or more if your paper is multidisciplinary and you have 10 co-authors... And even after all that has been done by the book, and you are absolutely sure that the manuscript is with the referees at last, you suddenly get another e-mail asking for the copyright form, informing you that the process won't go ahead until that is done and dusted... By the way, the last time I submitted a manuscript, after going through all that effort and stress, after a couple of days I got – out of the blue – a final e-mail from the journal saying that regrettably the manuscript was out of scope for the journal... one week wasted... So are we absolutely sure that the electronic submission system is more efficient than the old one? Sometimes – believe me – I'd rather use a homing pigeon than one of those websites... My feeling is that submitting manuscripts has become quite complicated for us authors, because certain Publishers have created monster submission systems that are all but user-friendly. It probably makes THEIR life easier, but certainly not OURS...

In this issue

Literature Coverage

- Palladium-Catalyzed Regioselective B–C(sp) Coupling via Direct Cage B–H Activation: Synthesis of B(4)-Alkynylated o-Carboranes** A177

Literature Coverage

- Charge-Transfer-Directed Radical Substitution Enables para-Selective C–H Functionalization** A180

Literature Coverage

- Exploiting the Distal Reactivity of Indolyl-methyl-enemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles** A184

Young Career Focus

- Young Career Focus: Professor Vittorio Pace (University of Vienna, Austria)** A189

Coming soon A192

Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

Clearly the above does not apply to Thieme Chemistry, whose submission system is human, efficient and user-friendly, by far the best on the market!!! And finally, let me introduce this new glittering SYNFORM issue, the last of the year! The first story covers a new chapter of the fascinating chemistry of carboranes, stemming from the labs of Z. Xie (P. R. of China). The second article describes a truly innovative reaction developed by T. Ritter (Germany/USA) for functionalizing arenes in para-position using TEDA and Pd catalysis. The third contribution originates from Italy where C. Curti and colleagues developed a synthesis of the ‘elusive’ dihydrocarbazoles using an organocatalyzed [4+2] cycloaddition. Last, but certainly not least, V. Pace (Austria) is the protagonist of a Young Career Focus interview.

Enjoy your reading!

Palladium Catalyzed Regioselective B–C(sp) Coupling via Direct Cage B–H Activation: Synthesis of B(4)-Alkynylated o-Carboranes

Chem. Sci. 2016, 7, 5838–5845

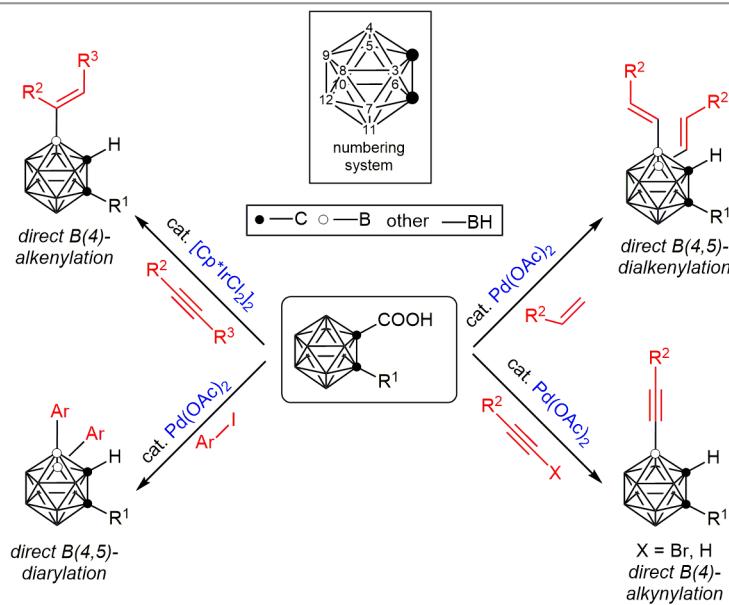
Icosahedral carboranes are a class of polyhedral boron hydride clusters in which one or more of the BH vertices are replaced by CH units, which can be viewed as three-dimensional relatives of benzene. Their exceptional thermal and chemical stabilities as well as 3D structures make them useful building blocks for boron neutron capture therapy agents in medicine, versatile ligands in coordination/organometallic chemistry, and functional units in supramolecular design/optoelectronic materials.¹ As a result, considerable attention has been directed towards the functionalization of carboranes.

Classic routes to functionalized carboranes rely on the polarized cage C–H/B–H bonds: the weakly acidic C–H proton ($pK_a \sim 23$) and basic B–H hydride.¹ Generally, cage C–H bonds can be deprotonated by strong bases, followed by the reaction with electrophiles to give carbon-substituted carboranes. Cage B–H bonds are preferentially subjected to electrophilic substitution reactions, resulting in the formation of cage boron-substituted carborane derivatives. However, the latter suffers from poor regioselectivity due to the presence of different electronic environments of BH vertices.

To tackle the regioselectivity problem, the group of Professor Zuowei Xie from the Chinese University of Hong Kong (P. R. of China) introduced a carboxyl group at the cage carbon to control the regioselectivity and facilitate cage B–H activation. Subsequently, transition-metal-catalyzed cage B(4)-alkenylation,^{2a} B(4,5)-dialkenylation,^{2b} and B(4,5)-diarylation^{2c} have been achieved (Scheme 1).

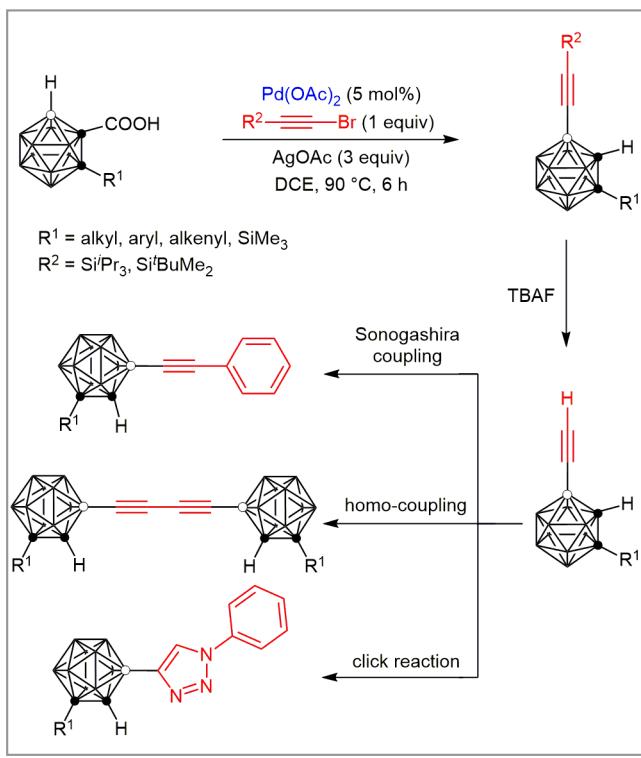
Professor Xie said: “In view of the wide application of carboranyl acetylenes in molecular rods, nanomaterials and metal-organic frameworks,¹ we have developed the first transition-metal-catalyzed regioselective cage B–C(sp) coupling via direct cage B(4)–H activation for the synthesis of B(4)-alkynylated o-carboranes.”

In the presence of 5 mol% $\text{Pd}(\text{OAc})_2$ and three equivalents of AgOAc , the reaction of carboranyl carboxylic acid with alkynyl bromide proceeds smoothly in DCE (DCE = 1,2-dichloroethane) at 90 °C to give the desired B(4)-alkynylated o-carboranes in moderate to very good isolated yields. Though this reaction is tolerant of many functional groups R^1 at the cage C(2), it is compatible only with sterically bulky silyl groups



Scheme 1 Carboxylic acid guided, transition-metal-catalyzed cage B–H functionalization

R^2 ," explained Professor Xie. He continued: "On the other hand, the silyl groups R^2 can be easily removed by treatment with TBAF (TBAF = tetra-*n*-butylammonium fluoride), giving quantitatively the terminal alkyne $4-(CH\equiv C)-2-R^1-o-C_2B_{10}H_{10}$. Like other terminal alkynes, this carboranyl acetylene is a useful synthon for the synthesis of a variety of *o*-carborane derivatives via Sonogashira coupling, homo-coupling and click reactions (Scheme 2)."

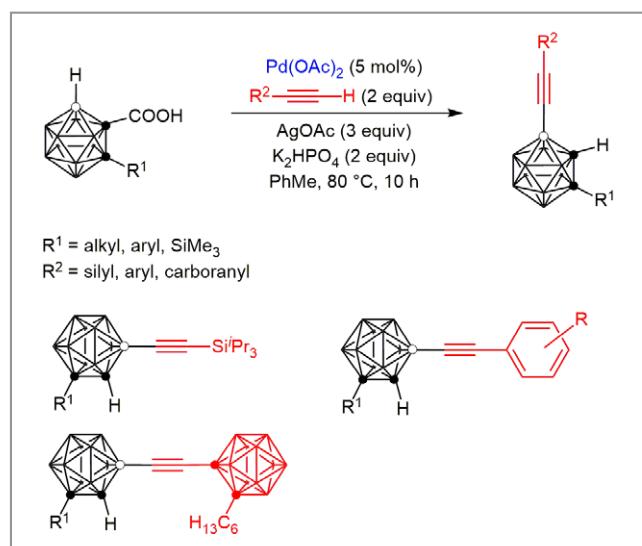


Scheme 2 Pd-catalyzed cage B(4)-H alkynylation using alkynyl bromides as coupling agents and subsequent transformations

"To broaden the substrate scope, another catalytic system, $Pd(OAc)_2/AgOAc/K_2HPO_4$, has been developed using terminal alkynes as coupling agents (Scheme 3)," remarked Professor Xie. He said: "Such an oxidative dehydrocoupling reaction is compatible with various R^2 groups like silyl, phenyl and carboranyl, leading to the preparation of different kinds of B(4)-alkynylated *o*-carboranes."

Professor Xie explained that preliminary mechanistic studies indicate (1) both catalytic cycles are initiated by $Pd(II)$ species, and (2) the traceless directing group $-COOH$ plays a key role not only in regioselectivity but also in monoselectivity of this reaction. Accordingly, two possible catalytic cycles involving $Pd(II)-Pd(IV)-Pd(II)$ and $Pd(II)-Pd(0)-Pd(II)$ proce-

ses were proposed for the aforementioned reaction systems, respectively.



Scheme 3 Pd-catalyzed cage B(4)-H alkynylation using terminal alkynes as coupling agents

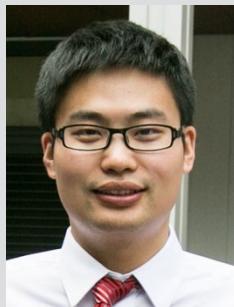
"In conclusion, two catalytic systems for regioselective cage B(4)-H alkynylation of *o*-carboranes have been developed, for the first time, via direct B-H activation, resulting in a variety of previously inaccessible cage B(4)-alkynylated *o*-carborane derivatives," said Professor Xie. "The current work represents significant advances over the known methods involving multi-step synthesis.³" He concluded: "This work also opens avenues to a wide and varied range of new carborane derivatives and sets an excellent example for the development of regioselective B-H functionalization in other boron clusters."

Mattes Tanke

REFERENCES

- (1) For selected reviews: (a) R. N. Grimes *Carboranes*, 2nd ed.; Academic Press: Oxford, 2011; (b) Z. Qiu, S. Ren, Z. Xie *Acc. Chem. Res.* **2011**, *44*, 299; (c) D. Olid, R. Núñez, C. Viñas, F. Teixidor *Chem. Soc. Rev.* **2013**, *42*, 3318; (d) M. Scholz, E. Hey-Hawkins *Chem. Rev.* **2011**, *111*, 7035.
 (2) (a) Y. Quan, Z. Xie *J. Am. Chem. Soc.* **2014**, *136*, 15513; (b) H. Lyu, Y. Quan, Z. Xie *Angew. Chem. Int. Ed.* **2015**, *54*, 10623; (c) Y. Quan, Z. Xie *Angew. Chem. Int. Ed.* **2016**, *55*, 1295.
 (3) (a) W. Jiang, D. E. Harwell, M. D. Mortimer, C. B. Knobler, M. F. Hawthorne *Inorg. Chem.* **1996**, *35*, 4355; (b) W. Jiang, C. B. Knobler, C. E. Curtis, M. D. Mortimer, M. F. Hawthorne *Inorg. Chem.* **1995**, *34*, 3491.

About the authors

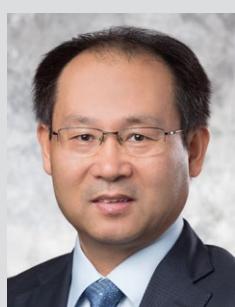


Dr. Y. Quan

Yangjian Quan received his B.Sc. from Nanjing University (P. R. of China, 2011) and his Ph.D. in chemistry from The Chinese University of Hong Kong (CUHK, P. R. of China, 2015) under the supervision of Professor Zuowei Xie. Currently, he is a research assistant professor in the Department of Chemistry, CUHK. He received the Hong Kong PhD Fellowship Award (2011–2015) and a Postgraduate Research Output Award (2014). His research interests include the development of new methodologies for the functionalization of carboranes and understanding of reaction mechanisms.



C. Tang



Prof. Z. Xie

Zuowei Xie received his Ph.D. in chemistry in 1990, working in a special joint program between the Shanghai Institute of Organic Chemistry (P. R. of China), Chinese Academy of Sciences (P. R. of China) and the Technische Universität Berlin (Germany). After a stay as a postdoctoral fellow at the University of Southern California (USA), he joined the chemistry faculty of CUHK (P. R. of China) in 1995, where he is now Choh-Ming Li Professor of Chemistry. He has received several prestigious awards including the State Natural Science Awards in 1997 and 2008, the Chinese Chemical Society Yao-Zeng Huang Award in Organometallic Chemistry in 2010, and the Croucher Award from the Croucher Foundation (Hong Kong) in 2003. He has co-authored over 260 publications and his recent work focuses on the chemistry of carboranes, supercarboranes, and metallacarboranes.

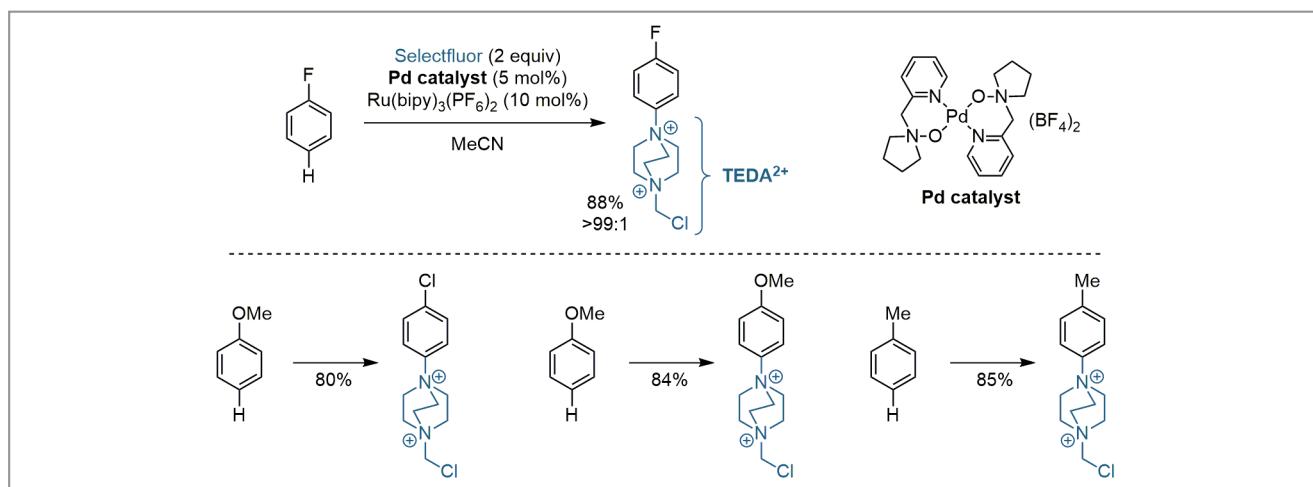
Charge-Transfer-Directed Radical Substitution Enables *para*-Selective C–H Functionalization

Nat. Chem. 2016, 8, 810–815

C–H bond functionalization continues to attract enormous interest from the synthetic organic chemistry community, as a response to the need for more atom-economical, environmentally benign and economically efficient chemical processes. The chelation-assisted approach for C–H functionalization is very successful and useful, and now a wide variety of Lewis basic functional groups can be made to provide chelation assistance through an appropriate choice of catalyst and conditions. However, the requirement for a specific group to promote a reaction in a specific position limits the potential substrate scope of such reactions. Unfortunately, when a coordinating directing group is not utilized, positional selectivity is nearly always lost, and multiple constitutional isomers are obtained as products. This selectivity issue hampers the utility of C–H functionalization significantly, because product mixtures imply a lower yield of the desired isomer, and waste in the form of the undesired ones. Therefore, C–H functionalization reactions that can afford high and predictable positional selectivity without the requirement for a particular directing group have the potential to be very powerful. Therefore, when the group of Professor Tobias Ritter from Harvard University (USA) and Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr (Germany) entered the field of C–H functionalization, they did so with the goal of developing useful C–H

functionalization reactions that would not require the use of coordinating directing groups to provide chelation assistance.

Professor Ritter explained: “We discovered the aromatic TEDAylation reaction quite by accident while attempting an oxidative C–H functionalization reaction with the electrophilic fluorinating reagent Selectfluor as oxidant. With fluorobenzene as substrate, we observed by ^{19}F NMR full conversion of the arene to a single product, but not the expected product, or any other product that we could readily imagine would arise from the reaction conditions. It took days for us to realize that the product was what we affectionately came to term an aryl-TEDA compound, arising from incorporation of the non-fluorine component of F-TEDA into the arene. That it took us so long to solve the mystery can be attributed partly to the unprecedented nature of such a reaction (direct cross-coupling of an aromatic compound to form a quaternary ammonium salt), and partly to the fact that Ar-TEDA compounds, because of their two positive charges, are difficult to observe with standard analytical tools of organic chemistry, such as thin-layer chromatography and GC/MS. These facts perhaps also explain why Ar-TEDA formation has not been discovered before, despite the fact that other groups have published other reactions with conditions that we have found to produce Ar-TEDA compounds.”

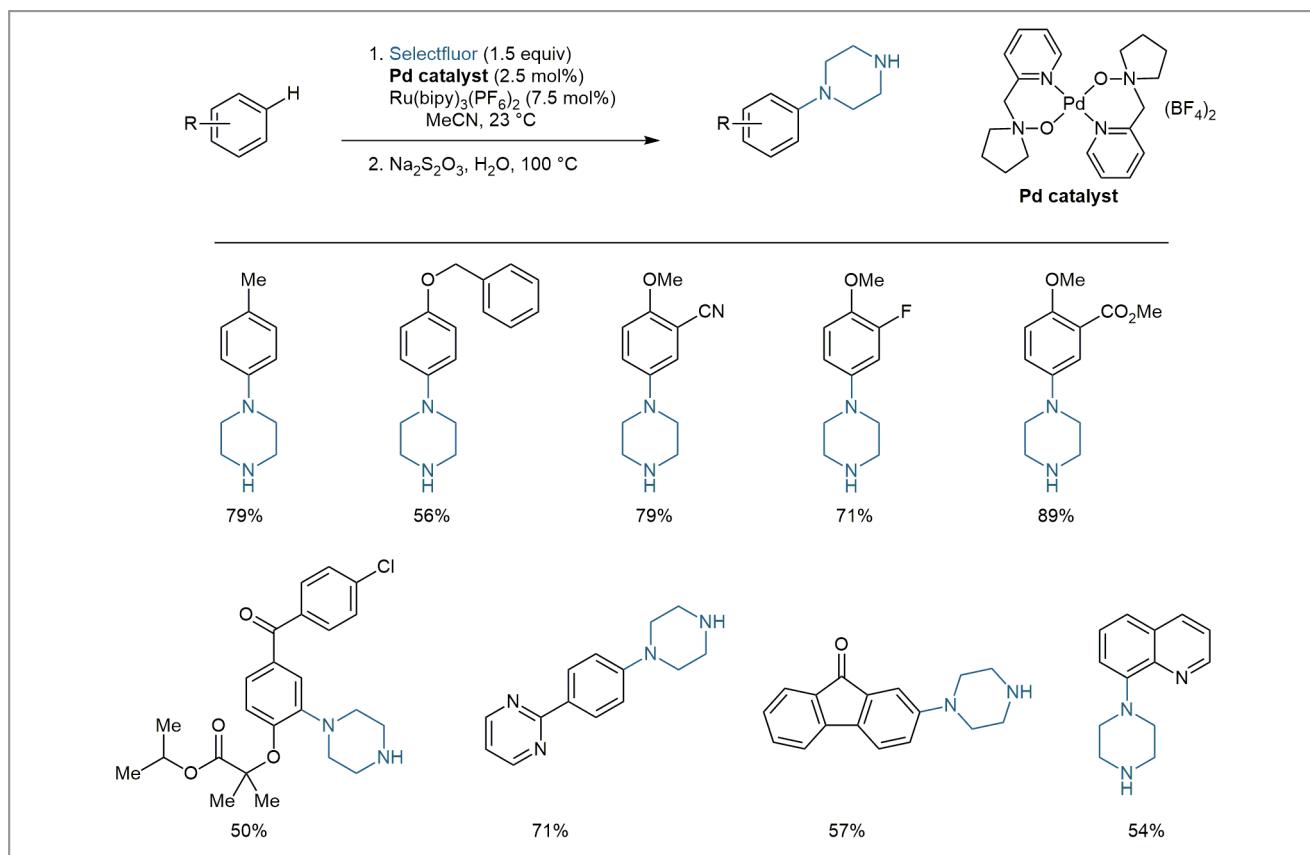


Scheme 1 Aryl-TEDA formation reaction exhibits high *para* selectivity for a variety of arenes

The group was delighted to find that nearly every simple arene they subjected to the same conditions led to a single product in high yield, which for monosubstituted arenes corresponded to the *para*-substituted isomer (Scheme 1). "Such a result is unprecedented in non-chelation-assisted C–H functionalization. However, Ar-TEDA products were a new class of compounds with no known application; thus, it was up to us to establish some utility for these strange new compounds," said Professor Ritter. He continued: "Fortunately, through much experimentation, we discovered that treatment of Ar-TEDA salts with sodium thiosulfate at elevated temperature affords aryl piperazines, which unlike Ar-TEDAs, are a very useful class of compounds, being a common motif in pharmaceuticals. We optimized a two-step, one-pot procedure that affords aryl piperazines in high selectivity directly from the corresponding C–H compound (Scheme 2). This method has the advantage over traditional syntheses of aryl piperazines in that it does not require a prefunctionalized starting material, such as an aryl bromide; crucially, this advantage relies on the high and predictable selectivity of the Ar-TEDA forma-

tion step. Thus, our new reaction went from a curiosity of fundamental reactivity to a potentially useful synthetic method."

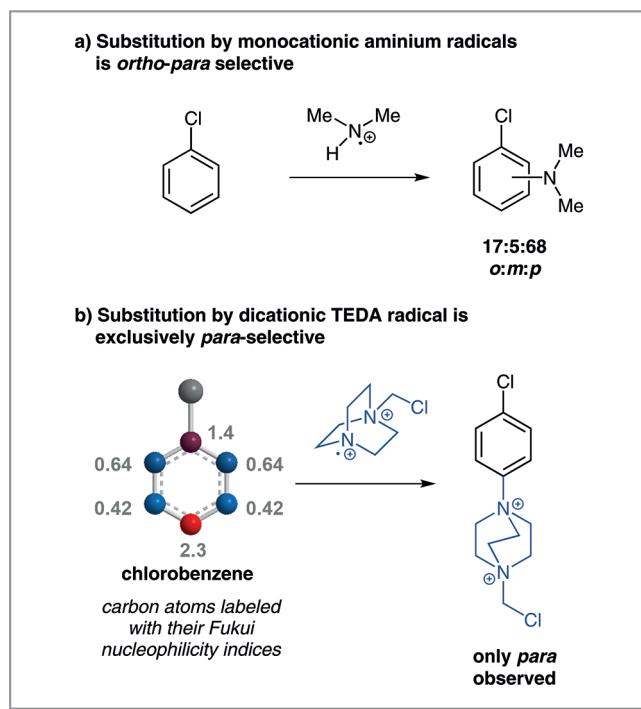
After months of reaction development, Professor Ritter and co-workers had yet to arrive at a convincing explanation for the remarkable *para* selectivity of the reaction. "We had already realized that the C–N bond formation likely occurred through radical aromatic substitution between the TEDA²⁺ radical and arenes, which is similar in kind to reactivity reported by Italian chemist Francesco Minisci in the 1960s," remarked Professor Ritter. Minisci noted that in contrast to aromatic substitution by neutral carbon-based radicals, which occur with very poor positional selectivity, substitutions by cationic aminium radicals exhibit higher selectivity, with electron-donating substituents directing substitution predominantly *ortho* and *para* to themselves. Professor Ritter commented: "This result is intuitive, as one would expect such electrophilic radicals to have selectivity similar to electrophilic aromatic substitution. What is harder to explain is why TEDA²⁺, with one more positive charge, exhibits such a high propensity to attack *para* to substituents, even at the expense of the



Scheme 2 Aryl-TEDA formation enables two-step, one-pot synthesis of aryl piperazines

ortho positions, which according to the basic model of electrophilic aromatic substitution are just as activated towards electrophilic attack as the *para* position.”

The breakthrough came with the realization that the *ortho* and the *para* positions differ significantly in their ability to donate electron density to incoming electrophilic species in the transition state of addition, as measured by Fukui nucleophilicity indices. “The realization that the *ortho* and *para* positions are thus electronically differentiated allowed us to argue that the selectivity of the reaction is controlled by arene-to-radical charge-transfer contribution to the transition state of addition; the contribution of such charge-transfer forms becomes more important with increasing electrophilicity of the radical, which is why adding an extra positive charge to a cationic aminium radical, as in the case of TEDA, leads to exclusive selectivity for the *para* position (Scheme 3),” explained Dr. Boursalian, a former graduate student with Ritter and first co-author of the paper.

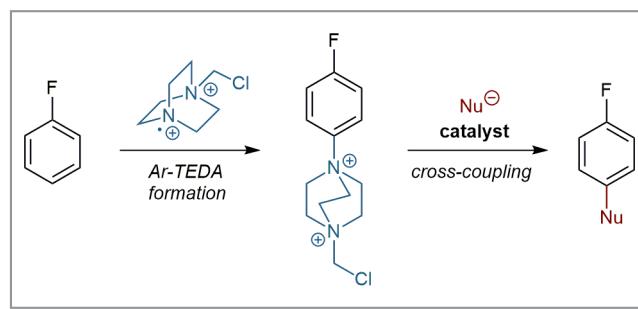


Scheme 3 The additional positive charge on TEDA^{2+} leads to increased *para* selectivity over substitution by monocationic aminium radicals. The *para* selectivity is predictable by Fukui nucleophilicity indices.

“One corollary to our proposal is that highly *para*-selective radical additions are not in principle limited to the TEDA^{2+} radical,” said Professor Ritter. He continued: “Potentially any ra-

dical of sufficiently high electron affinity can afford very high *para* selectivity, and incorporation of multiple positive charges is the best way to increase the electron affinity of a radical. The challenge then becomes designing stable precursors that can reliably generate such highly electrophilic radicals under conditions relevant to organic synthesis. Work in our group is underway to identify such precursors, which can act as convenient reagents for *para*-selective functionalization of arenes to useful products.”

“Another direction we are exploring is to find applications for the unusual and unprecedented class of Ar-TEDA compounds beyond the synthesis of aryl piperazines. One enticing possibility that we are currently investigating is the use of Ar-TEDA compounds as cross-coupling electrophiles, with the TEDA moiety acting as a pseudohalide,” said Professor Ritter. He concluded: “If a catalyst can be found that can cleave the Ar-TEDA bond, then in principle cross-coupling should be possible with an arbitrary nucleophile, opening the way to a general, two-step sequence for *para*-selective C–H functionalization (Scheme 4).”



Scheme 4 Potential application of Ar-TEDA compounds as cross-coupling electrophiles

Matten tanke

About the authors



Prof. T. Ritter

Tobias Ritter was born in 1975 in Lübeck (Germany) and studied in Braunschweig (Germany), Bordeaux (France), Lausanne (Switzerland), and Stanford (USA). After research with Professor Barry M. Trost at Stanford, he obtained his Ph.D. working with Professor Erick M. Carreira at ETH Zurich (Switzerland) in 2004. He then carried out postdoctoral research with Professor Robert H. Grubbs at Caltech (USA). In 2006, he was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard University (USA), promoted to Associate Professor in 2010, and to Professor of Chemistry and Chemical Biology in 2012. He is also a faculty member at the Massachusetts General Hospital (USA) in the Department of Radiology. In 2015, Tobias Ritter became a Director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany). He currently maintains groups in Mülheim and in Cambridge (USA).



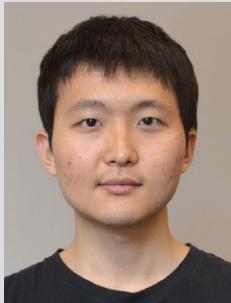
Dr. G. Boursalian

in 2010 as an NSF Predoctoral Fellow, and joined the group of Professor Tobias Ritter shortly thereafter. He graduated in May 2016, having spent the final year of his graduate studies at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany), where Professor Ritter has moved his group. His doctoral thesis is entitled ‘Reactivity and Selectivity in C–H Functionalization by Electrophilic Radicals.’



Dr. A. R. Mazzotti

Anthony R. Mazzotti was born in Taylorville, IL (USA) in 1988 and received his B.S. degree in chemistry in 2010. He obtained his Ph.D. in 2016 from Harvard University (USA), where he worked on the fluorination of arylboronic acid derivatives and selective arene C–H functionalization with Tobias Ritter. During his studies, he was awarded both the Barry M. Goldwater Scholarship and the National Science Foundation Graduate Research Fellowship.



W. S. Ham

Won Seok Ham was born in Anyang, Gyeonggi-do (South Korea) in 1991. He received his B.A. degree in biochemistry at Columbia University in New York City (USA). In 2013, he joined the group of Professor Tobias Ritter as a Ph.D. student at Harvard University (USA). Won Seok is a recipient of the Doctorate Scholarship from Kwanjeong Educational Foundation. A major focus of his research is the development of practical, selective aromatic C–H functionalization.

Exploiting the Distal Reactivity of Indolylmethylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

Chem. Eur. J. 2016, 22, 12637–12640

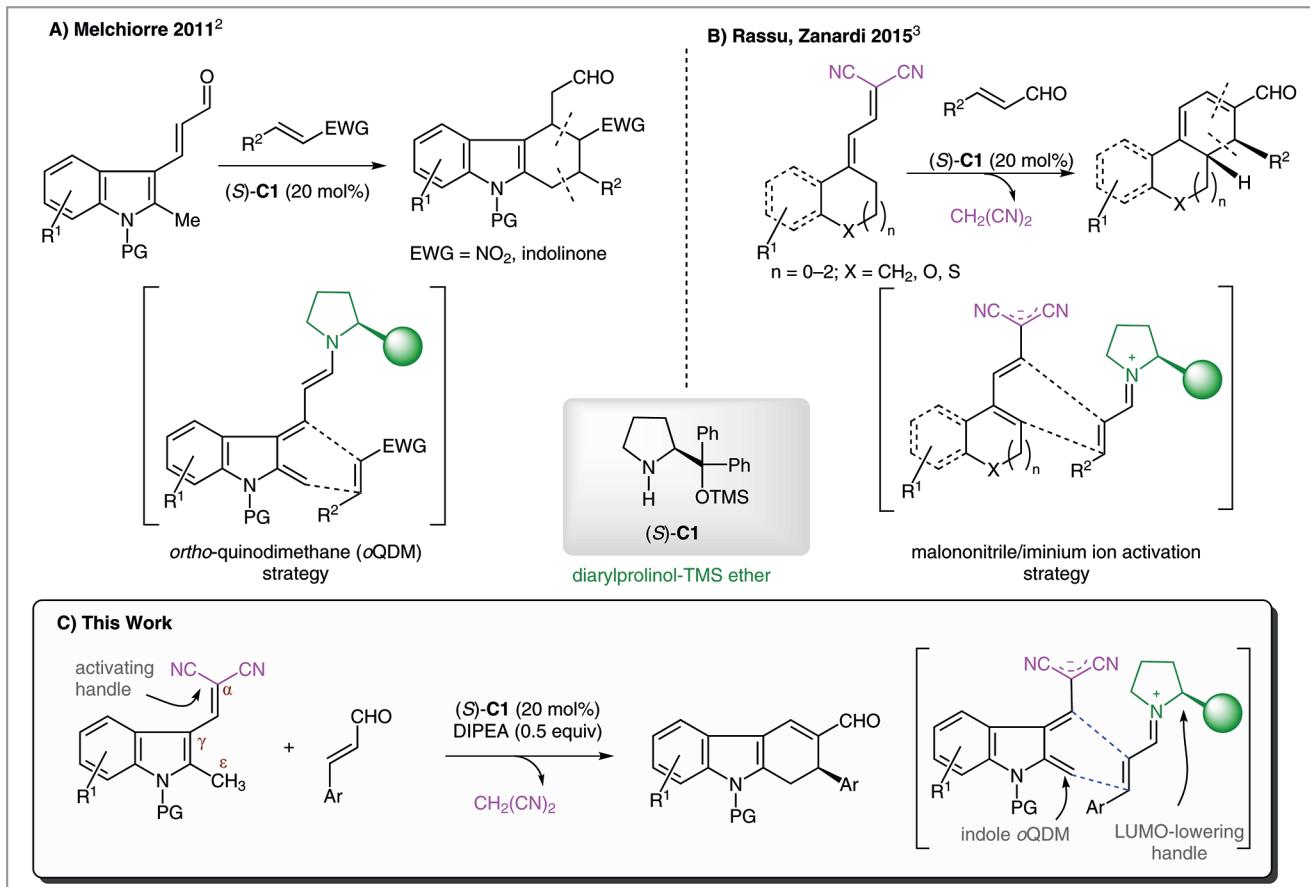
Since the advent of modern organocatalysis at the turn of the 21st century, asymmetric aminocatalysis, which uses chiral amines as catalysts, has been at the center of an explosive growth, culminating in the implementation of a myriad of high-impact stereoselective organic transformations, many of which are represented by efficient and creative organocatalytic formal [4+2] cycloadditions.¹ In particular, the use of aminocatalysts proved to be an extremely useful strategy to induce the transient generation of highly reactive *ortho*-quinonodimethane (oQDM) intermediates from simple heteroaromatic compounds (e.g., methylindole-, methylpyrrole- or methylfuran-based heterocycles) while directing the pericyclic reactions with suitable dienophiles toward a highly stereoselective pathway. “Our approach provides straightforward access to complex, chiral polycyclic architectures, which would be difficult to synthesize by other catalytic methods, and should open new synthetic pathways to complex chiral molecules using nontraditional disconnections. The paper in *Chem. Eur. J.* is the result of a fruitful collaboration between two research groups: a group from the Università degli Studi di Parma (Italy), led by Professor Franca Zanardi, and their colleagues of the Consiglio Nazionale delle Ricerche (CNR) in Sassari (Italy), led by Dr. Gloria Rassu,” said Professor Claudio Curti from the group in Parma, adding: “In this context, in 2011, we read with interest the work published by Melchiorre and co-workers² in which he reported a reliable synthetic strategy to access tetrahydrocarbazoles by adopting a [4+2] disconnection which relies on the *in situ* generation of active indole *ortho*-quinonodimethane intermediates (oQDM) in reactions with suitable dienophiles (e.g., nitrostyrene or indolinone derivatives) under trienamine catalysis (Scheme 1A). During that period,” continued Professor Curti, “we were focusing on the search for new, extended pro-nucleophilic structures, to be activated and exploited as polyenolate nucleophiles in organocatalytic, enantioselective vinylogous and hypervinylogous transformations. This search ended in 2015 with the discovery of a new, direct [4+2] eliminative cycloaddition modality to access chiral, polyfunctionalized carbocycles embedding fused cyclohexadiene frames by the use of remotely enolizable π -extended allylenemalononitriles as

electron-rich 1,3-diene precursors with both aromatic and aliphatic α,β -unsaturated aldehydes under iminium ion driven organocatalysis (Scheme 1B).³

Inspired by these newly disclosed processes and mindful of Melchiorre’s work, the groups involved in this collaboration wondered whether the use of the malononitrile activation strategy could also be applied to methylindole-based scaffolds. Professor Curti said: “It was while discussing these issues with Professor Giovanni Casiraghi, our inspiring mentor – actually, Professor Giovanni Casiraghi retired in 2010 but he continued to enthusiastically discuss chemistry with us until his recent death, on July 21, 2016 – that the idea came up: *Why don’t we try to merge our malononitrile activation strategy with the indole *ortho*-quinonodimethane modality by reacting 2-methylindole-based methylenemalononitriles and enals with the aid of a chiral secondary amine catalyst?*”

The authors reasoned that, if viable, this strategy would lead to interesting chiral, enantiopure, polyfunctionalized 2,9-dihydro-1*H*-carbazole-3-carboxaldehydes through a direct, domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade that could be envisaged as a formal [4+2] cycloaddition.

Initially, a set of experiments evaluating the feasibility of the transformation between *N*-Boc-protected 2-methylindolylmethylenemalononitrile and cinnamaldehyde promoted by a series of chiral, secondary amine catalysts were performed by Dr. Rassu in Sassari. “Pleasingly, Dr. Rassu found that promising results were obtained with the use of the popular Hayashi-Jørgensen α,α -diphenylprolinol trimethylsilyl ether catalyst (*S*)-**C1** that promoted the formation of the corresponding dihydrocarbazole adduct with exceptional enantioselectivity (99% ee), albeit in only moderate yields,” explained Professor Curti. He continued: “We soon discovered that a competing retro-Knoevenagel reaction on the starting pro-nucleophilic methylenemalononitrile hampered the completion of the process, and variable amounts of related aldehyde precursors were detected in the crudes. Meticulous optimization of the reaction conditions (e.g., the use of DIPEA instead of Et₃N, and the fine-tuning of the nucleophile/electrophile molar ratio) allowed us to solve this problem, and a viable reaction with



Scheme 1 Merging the *o*QDM strategy with the malononitrile/iminium ion activation strategy toward the synthesis of chiral, enantiopure 2,9-dihydro-1*H*-carbazole 3-carboxaldehydes

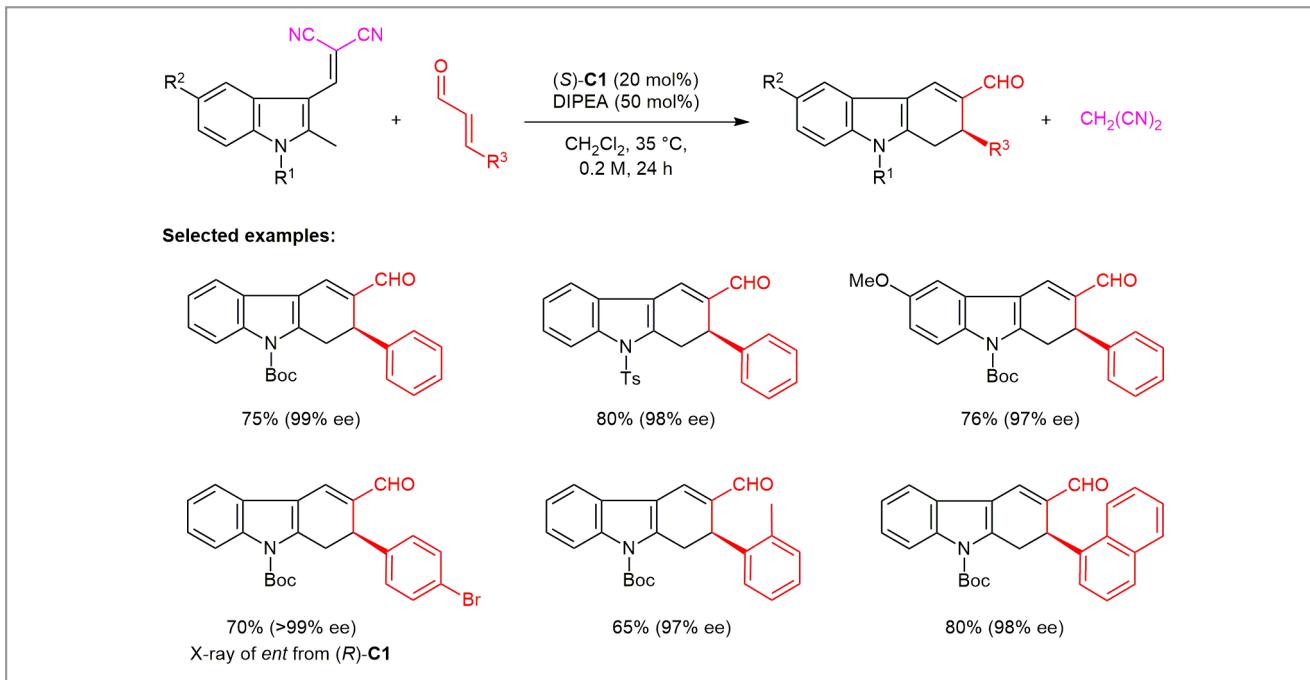
improved isolated yield and very high enantioselectivity was finally at hand."

Professor Curti revealed that the reaction performed directly on the parent aldehyde precursor (in which the malononitrile group is missing) completely failed, highlighting the fundamental role exerted by the malononitrile moiety as activating handle of the nucleophilic indole counterpart.

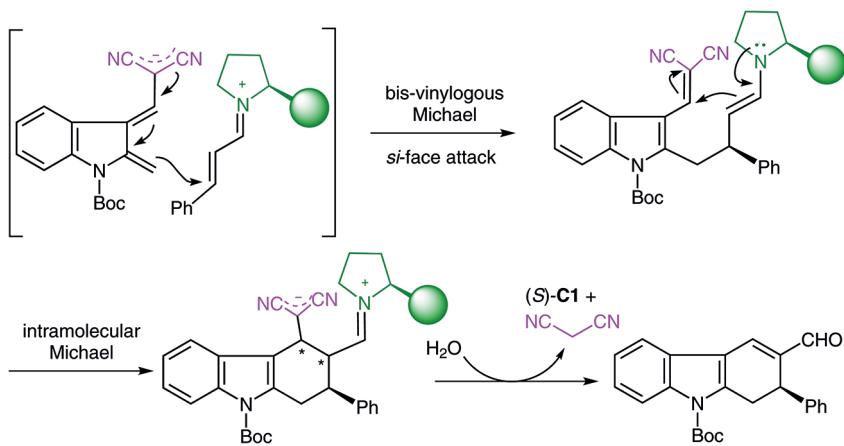
"The scope and limitations of this [4+2] eliminative cycloaddition utilizing diversely substituted methylenemalononitriles and enals were then examined both in Parma and Sassari: it was found that the core structure of the formed formyl dihydrocarbazoles could be readily decorated at different positions without having a detrimental effect on either yield or enantioselectivity," said Professor Curti. Also, varied substituents at the aromatic moiety of the olefinic aldehyde derivatives were tolerated, regardless of their position and electronic properties. Professor Curti continued: "Interestingly, only electron-poor *N*-Boc-, *N*-Moc-, and *N*-Ts-protected indoles

proved to be reliable substrates for this transformation, while the electron-rich *N*-Me derivative was completely inactive. This prompted us to invoke a direct correlation between the electronic nature of the *N*-protecting group and the pK_a of the enolizable CH_3 ."

To achieve a better understanding of the reaction mechanism and transition states involved in this process, the absolute configuration of the dihydrocarbazole targets needed to be unveiled. Professor Curti explained: "Actually, since these scaffolds were quite unique and unprecedented, we couldn't find any structural correlation with known, stereodefined products, and X-ray crystallographic analysis of suitable crystals remained our only option." He continued: "Fortunately, after several attempts, we succeeded in obtaining good crystals of the p-bromocinnamaldehyde derivative obtained with catalyst (*R*)-C1; and in collaboration with Professor Giorgio Pelosi of the Department of Chemistry of the University of Parma we were able to unambiguously assign the (2*S*)-configuration



Scheme 2 Enantioselective iminium ion mediated [4+2] eliminative cycloaddition: selected examples



Scheme 3 Crucial reaction steps involved in the domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade

of the sample by X-ray crystallographic analysis (consequently the 2*R*-configuration was assigned to all compounds derived from catalyst (*S*)-C1). With these data at hand, Professor Curti and collaborators were able to propose a stepwise reaction mechanism for the key [4+2]: a domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade in which the crucial enantioselective step resides in the attack of the nucleophilic methylene carbon of the indole *o*QDM intermediate

to the *si*-face of the iminium ion derived from covalent association of the enal to the prolinol catalyst (*S*)-C1.

Professor Curti concluded: "This work represents our last advancement in the field of organocatalysis: further studies to apply the malononitrile/iminium ion activation strategy in the vinylogous realm is ongoing in our laboratories and will be disclosed in due course."

Martes Tandem

About the authors



Prof. C. Curti

Claudio Curti is Assistant Professor of Organic Chemistry at the University of Parma (Italy), Department of Pharmacy. He earned his Laurea degree in Pharmaceutical Chemistry and Technology in 2002 at the University of Parma. In 2005, he graduated from the postgraduate School of Chemical Synthesis at the University of Milan (Italy). In 2001, he joined the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma) under the supervision of Professor Giovanni Casiraghi, where he would eventually take up his current position. His main research interests are in the field of asymmetric synthesis and organic chemistry methodology, focusing on the development of metal- and organocatalytic, enantioselective vinylogous and hypervinylogous processes and their exploitation in the synthesis of multifunctional natural and natural-like compounds, including densely functionalized heterocycles and polyphenol metabolites.



Dr. G. Rassu

Gloria Rassu is Research Executive at the Consiglio Nazionale delle Ricerche (CNR), Istituto di Chimica Biomolecolare (Sassari, Italy). She was born and raised in Sassari (Italy) and earned her Laurea degree in chemistry at the University of Sassari (Italy) in 1979. After five years postdoctoral work, she joined the research group of Professor Giovanni Casiraghi working on the development of a novel vinylogous aldol methodology and its exploitation in the total synthesis of densely functionalized chiral compounds. In 2001, she was promoted to First Researcher position and in 2002 she took up her present rank at the CNR. Her main scientific interests reside in the design and application of new catalytic, enantioselective, vinylogous processes toward the synthesis of biologically active molecules such as carbohydrate mimetics, nucleoside analogues, modified and conformationally constrained amino acids and glycopeptidomimetics for integrin receptor targeting.



N. Brindani

Nicoletta Brindani was born in Borgo Val di Taro, Parma (Italy) in 1988. She studied medicinal chemistry and technology at the University of Parma, where she received her Laurea degree in 2012. At present she is a PhD student of food science under the supervision of Professor Daniele Del Rio and Professor Claudio Curti working in the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma). Her research interests, centered in the field of organic synthesis, are focused toward the development of new asymmetric, vinylogous, and organocatalytic methodologies for the total synthesis of chiral bioactive molecules.



Dr. V. Zambrano

Vincenzo Zambrano was born in 1972 in Sassari (Italy). He obtained his degree in chemistry from the University of Sassari (Italy) in 1997 (supervisor: Professor Giovanni Minghetti). In 2003, he received his Ph.D. in chemistry from the University of Sassari (supervisors: Drs. Gloria Rassu and Luigi Pinna), working on the synthesis of a very large collection of carbasugars. In 2008, he became Technologist at the Istituto di Chimica Biomolecolare of CNR in Sassari. His research interests are focused on the stereoselective synthesis of bioactive molecules of natural and unnatural origin. He deals with the characterization and structural determination of organic compounds using one- and two-dimensional NMR techniques, in particular 1D (¹H NMR, ¹³C NMR) and 2D (Cosy, Tocsy, HMQC and Noesy).



Dr. L. Pinna

Luigi Pinna was born in Sassari (Italy) in 1961. He graduated in chemistry from the University of Sassari (Italy) in 1987 and obtained his Ph.D. in chemical sciences from the same university in 1992. In 1990, he was the winner of an open selection for university researchers and since 1993 he has been a confirmed researcher at the Department of Chemistry and Pharmacy of the University of Sassa-

>>

ri. He is currently collaborating with the Bio-Organic Synthesis group of Department of Pharmacy of the University of Parma, and the Institute of Biomolecular Chemistry (ICB) of CNR (Sassari, Italy). His main scientific interests reside in the development of new, catalytic, enantioselective, vinylogous processes toward the synthesis of biologically active molecules.



Prof. G. Pelosi

Giorgio Pelosi graduated from the University of Parma (Italy) in 1987 and obtained his Ph.D. in 1991 from the same institution under the mentorship of Professor Mario Nardelli, at the time President of the International Union of Crystallography. During his Ph.D. he had the chance to develop skills in protein crystallography at the University of Pavia (Italy) under the supervision of Professor Martino Bolognesi. Then, he did postdoctoral research for one year at the Laboratory of Molecular Biophysics of the University of Oxford (UK) in the group of Professor Sir Jack Baldwin, supervised by Professor Janos Hajdu. He returned to the University of Parma where he was appointed Associate Professor in 1998. His research interests are in the chemistry of biologically active metal-containing compounds and structural chemistry based on X-ray crystallography.



Prof. F. Zanardi

Franca Zanardi is currently an Associate Professor of Organic Chemistry at the Department of Pharmacy, University of Parma (Italy). She received her Laurea degree in chemistry (1993) and her Ph.D. in bioorganic chemistry (1997) from the same university under the direction of Professor Giovanni Casiraghi. She became an Assistant Professor in 1998 and Associate Professor in 2002. Currently she leads the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma). Her research interests concern the development of stereoselective, vinylogous, and hypervinylogous methodologies addressed at the synthesis of biologically relevant chiral nonracemic molecules in the bioorganic and pharmaceutical domains. She is also involved in several research programs aimed at the synthesis and applications of biologically relevant pseudopeptides to be exploited as therapeutic/diagnostic tools in various diseases.

REFERENCES

- (1) *Comprehensive Enantioselective Organocatalysis*, Vol. 1–3; P. I. Dalko, Ed.; Wiley-VCH: Weinheim, 2013.
- (2) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre *J. Am. Chem. Soc.* **2011**, *133*, 15212.
- (3) N. Brindani, G. Rassu, L. Dell'Amico, V. Zambrano, L. Pinna, C. Curti, A. Sartori, L. Battistini, G. Casiraghi, G. Pelosi, D. Greco, F. Zanardi *Angew. Chem. Int. Ed.* **2015**, *54*, 7386.

Young Career Focus: Professor Vittorio Pace (University of Vienna, Austria)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Vittorio Pace (University of Vienna, Austria).

Biographical Sketch



Prof. V. Pace

Vittorio Pace obtained a degree in Pharmacy from the University of Perugia (Italy) in 2005. He then undertook PhD studies (2006–2010) at the Complutense University of Madrid (Spain) under the guidance of Professors A. R. Alcántara and J. V. Sinisterra. He realized placements at the Universities of Ghent (Belgium, Professor N. De Kimpe), Trieste (Italy, Professor L. Gardossi) and Graz (Austria, Professor W. Kroutil). In 2009, he also obtained a postgraduate MSc in Drug Design and Development from the University of Pavia (Italy). In 2010, he moved to the University of Vienna (Austria) to join the group of Professor W. Holzer as a Mach postdoctoral fellow. Postdoctoral training continued with Professor D. J. Procter at The University of Manchester (UK, 2011–2013) and with Professor B. Olofsson at Stockholm University (Sweden, 2013–2014). In August 2014, he came back to Vienna as a group leader in Synthetic Chemistry at the Department of Pharmaceutical Chemistry. In November 2014, he obtained a habilitation for Associate Professor of Organic Chemistry by the Italian Ministry of Education. In 2015, he was awarded with the Vincenzo Caglioti Prize by the Accademia Nazionale dei Lincei, the Ciamician Medal by the Division of Organic Chemistry of the Italian Chemical Society and the Young Investigator Award by the Faculty of Life Sciences of the University of Vienna. In May 2016, he submitted his Habilitation Thesis for the *venia docendi* at the University of Vienna. His main research interest deals with the application of lithium carbenoids and organometallic reagents in organic synthesis.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. V. Pace My group is working on the development of novel synthetic strategies based on the use of particular functionalized reagents, as metal (mainly lithium and magnesium) carbenoids are. In particular, we look at performing homologation-type reactions which constitute highly versatile tools in synthetic medicinal chemistry. Strong attention is devoted to establishing reaction conditions able to exploit the nucleophilic behavior of such ambiphilic reagents with the aim of designing fully chemoselective processes. The systematic study of the reactivity of these reagents with electrophilic partners such as carbonyl derivatives allowed us to describe new protocols for formally inserting functionalized C_1 -synthons. More recently, our interest encompassed the use of chiral organolithium reagents and hydride nucleophiles in analogous nucleophilic additions.

SYNFORM *When did you get interested in synthesis?*

Prof. V. Pace During my undergraduate studies in Pharmacy at the University of Perugia (Italy) I felt a particular interest towards organic synthesis, culminating in realizing my MSc thesis under the direction of Professor Curini and Dr. Rosati. Later on, I started my PhD at the Complutense University of Madrid with Professors Alcantara and Sinisterra on integrated approaches towards α -haloketones as prochiral precursors of biologically active structures. During my PhD I had the opportunity to visit the lab of Professor De Kimpe at Ghent University (Belgium) where I got to work with diazomethane-based homologations and therein I started to think about embarking on a postdoctoral experience on synthetic methods. Just after defending my PhD, I did postdoctoral training in Austria (with Professor Holzer), the UK (with Professor Procter) and Sweden

(with Professor Olofsson) and after four years I went back to the University of Vienna as a group leader in synthetic chemistry.

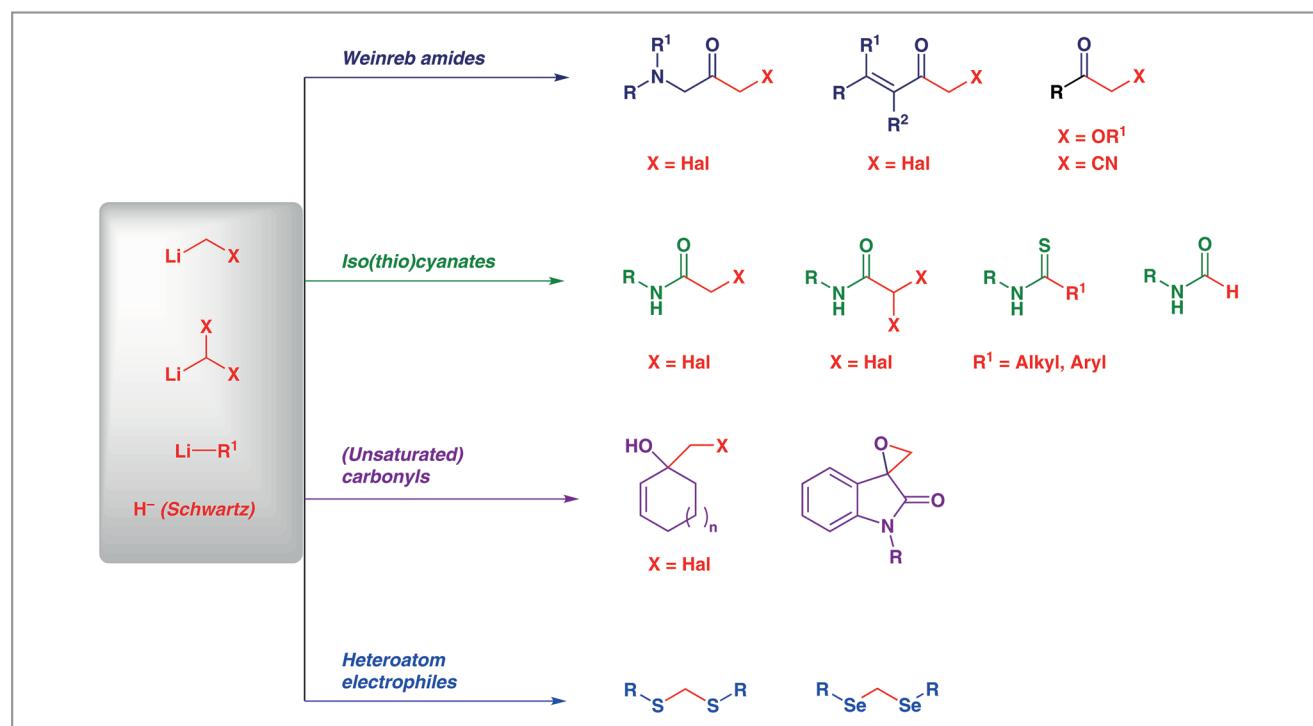
SYNFORM What do you think about the modern role and prospects of organic synthesis?

Prof. V. Pace Organic synthesis plays a pivotal role in modern chemistry and biology: there is almost no possibility of providing society with pharmacologically active substances without it. As such we should all be conscious of its fundamental importance in science. Nowadays, we have excellent tools for assembling complex molecules which, unfortunately, are often regarded as non-environmentally friendly despite their undoubtable efficiency: in my opinion, this concept should be demystified and redefined in the broad context of what synthetic chemistry is able to provide. Moreover, profound chemical education is required for generating a new class of chemists able to develop strategies based not only on recently reported techniques but also keeping an eye on old literature, which represents a precious source of inspiration. I hope to have fully demonstrated this concept in my Habilitation thesis entitled “*New Perspectives in Homologation Processes for Synthetic Medicinal Chemistry: Lithium Halocarbenes*” submitted at the University of Vienna in May 2016.

oids at the Helm” submitted at the University of Vienna in May 2016.

SYNFORM Your research group is active in the area of organic synthesis, medicinal chemistry and drug design. Could you tell us more about your research and its aims?

Prof. V. Pace My group has two main research lines strictly connected: 1) synthetic methodology and 2) synthetic medicinal chemistry. This last topic is conducted in collaboration with colleagues active in drug design and modeling operating in our department (Professors Langer and Ecker), who provide us with lead compounds to be synthesized. On the other hand, the development of synthetic methodology is very important for us since it allows us to establish and design protocols of general usefulness for the scientific community. The study of reaction mechanisms and the trapping of intermediates occupy a central place in our investigations. The deep understanding of a given process enables us to control and modulate the reactivity with the final aim of maximizing the chemical efficiency. In this context, I am grateful to our NMR specialists – Professors Holzer and Urban – for the admirable advice in elucidating mechanisms. Furthermore, we consider it highly significant and productive to apply our developed method-



Scheme 1 Overview of homologation and related processes developed in Pace’s group

ologies to the synthesis of important scaffolds (e.g. intermediates required in drug synthesis), or even to employ recently reported chemistry to one of our synthesized materials with the aim of exploiting both the synthetic potential and appeal. In conclusion, I believe our success depends both on the fruitful collaborations within the department, and the motivation and dedication my students put in their daily work. Thanks to Laura Castoldi, Serena Monticelli, Karen De la Vega, Marta Rui, Vanna Parisi, Azzurra Pelosi, Irene Murgia...*inter alia*.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. V. Pace Since we started some years ago, our research on the use of organolithium reagents has received good international visibility, as also demonstrated by highlights appearing in *Synfacts* or *Org. Process Res. Dev.* The reactivity of these reagents with heterocumulenes (isocyanates and iso-thiocyanates) is, in my opinion, our most impactful achievement since we have been able to form new functionalized C–C or C–H bonds through a single synthetic step. In such a way, (thio)amide derivatives could be assembled in very high yields and, in the case of using enantiopure reagents, in excellent enantiomeric ratios. Effectively, the reactivity of heterocumulenes towards organometallic reagents is so high because of the practically negligible electronic and steric effects played by the substituent at nitrogen. Remarkably, we smoothly prepared a wide library of thioamides in a conceptually different and more efficient approach to the classical ones based on thionation procedures, the drawbacks of which, such as harsh conditions or bad smells, are well known among chemists.

Marta Rui

Coming soon

SYNTHESIS Highlight

Diastereoselective Gold(I)-Catalyzed [2+2+2] Cycloaddition of Oxo-1,5-enynes

Literature Coverage

Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand

Literature Coverage

Copper-Mediated Oxidative Fluorination of Aryl Stannanes with Fluoride

Further highlights

Synthesis Short Review: Recent Developments in the Chemistry of Vinylsiloxanes

(by O. Riant and co-workers)

Synlett Account: Benziodoxol(on)e Reagents as Tools in Organic Synthesis: The Background behind the Discovery at the Laboratory of Catalysis and Organic Synthesis

(by J. Waser)

Synfacts Synfact of the Month in category “Organo- and Biocatalysis”: Highly Enantioselective Addition of Allyltrimethylsilane to Aldehydes

For current SYNFORM articles, please visit www.thieme-chemistry.com
SYNFORM issue 2017/01 is available from December 19, 2016
at www.thieme-connect.com/ejournals

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office

- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
- Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
- Assistant Scientific Editor: Kathrin Ulbrich, kathrin.ulbrich@thieme.de, phone: +49 711 8931 785
- Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Helene Ott, helene.ott@thieme.de, phone: +49 711 8931 929
- Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Senior Marketing Manager: Julia Stötzner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
- Postal Address: Synthesis/Synlett/Synfacts, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information

Synform will be published 12 times in 2016 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Via e-mail: customerservice@thieme.com
Via website: www.thieme-chemistry.com
Phone: +1 212 760 0888; Fax: +1 212 947 1112
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Via e-mail: customerservice@thieme.de
Via website: www.thieme-chemistry.com
Phone: +49 711 8931 421; Fax: +49 711 8931 410
Current list prices are available through www.thieme-chemistry.com.

Online Access

The online versions of Synform as well Synthesis, Synlett and Synfacts are available through www.thiemeconnect.com/products/ejournals/journals where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone +91 120 45 56 600
Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to Synthesis and Synlett

Manuscript submissions will be processed exclusively online via <http://mc.manuscriptcentral.com/synthesis> and <http://mc.manuscriptcentral.com/synlett>, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart - New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.